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Flecainide and Amiodarone Interaction

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Oral amiodarone therapy was given to seven patients already taking oral flecainide regularly. In one additional patient, administration of flecainide was temporarily discontinued when amiodarone therapy was begun, and then resumed. Amiodarone produced a rise in mean dose-adjusted flecainide plasma level (trough plasma level at steady state/daily dose) from 2.3 ± 0.8 to 3.4 ± 0.9 (ng/ml)/(mg/day) ($p < 0.01$). Accordingly, the mean dose of flecainide required to maintain similar plasma levels of the drug was one-third lower during combined treatment than during therapy with flecainide alone. This drug interaction must be accounted for when amiodarone and flecainide are used concomitantly.

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Flecainide and amiodarone are antiarrhythmic agents with dissimilar electrophysiologic and pharmacokinetic properties (1,2). Each is known to be efficacious in suppressing various cardiac arrhythmias and their use in combination may, in some cases, have an enhanced antiarrhythmic effect. Amiodarone has been reported to have kinetic interactions with multiple cardiac and noncardiac drugs, including digoxin, quinidine, procainamide, aprindine, phenytoin and warfarin sodium (3). Our findings in eight patients who received flecainide and amiodarone in combination suggest that an interaction also exists between these two drugs.

Methods

Study group. Six men and two women, 40 to 70 years old (mean 58), were referred to the Jewish Hospital at Washington University Arrhythmia Service for management of sustained ventricular tachycardia (three patients), aborted sudden cardiac death syndrome (three patients), syncope (one patient) and recurrent atrial flutter with pre-excitation (one patient). Seven patients had coronary artery disease and one had rheumatic heart disease, which was treated with mitral valve replacement and tricuspid commissurotomy several years earlier, and ventricular pre-excitation. All patients had some degree of left ventricular dysfunction, and the left ventricular ejection fraction, measured with radionuclide gated ventriculography in seven patients, ranged between 21 and 49% (mean 37). Blood urea nitrogen and creatinine levels were normal and remained stable throughout the study in all patients. These patients had all been treated with commercially available drugs without satisfactory results, or with intolerable adverse effects.

Drug administration. Treatment began with oral flecainide in two divided doses daily, at an initial dose of 200 mg daily. Doses were increased by 100 mg daily at 4 day intervals, guided by antiarrhythmic effects, changes in QRS complex duration on the 12 lead electrocardiogram, emergence of drug intolerance and plasma drug levels (ng/ml). In all patients who had ventricular tachycardia, the decision to add amiodarone to the therapeutic regimen was based on a partial antiarrhythmic effect from flecainide alone, measured by electrophysiologic testing performed during steady state treatment with maximal tolerated doses. The patient with rheumatic heart disease received amiodarone when it was observed that flecainide was successful in eliminating ventricular pre-excitation, but not atrial flutter. Amiodarone administration consisted of a 10 to 14 day oral loading period using 1,200 mg daily, divided into three equal doses, after which the dose was decreased to 600 mg daily. When amiodarone was added, flecainide was usually decreased arbitrarily by one-third to one-half of the previous dose in anticipation of a possible interaction. This practice was reinforced by the observation, in Patient 2, of the development of left bundle branch block 4 days after the beginning of treatment with amiodarone; a similar change in the electrocardiogram had been noted during flecainide monotherapy when the plasma level was 920 ng/ml. Because of the inordinately prolonged half-life of amiodarone, serial amiodarone plasma

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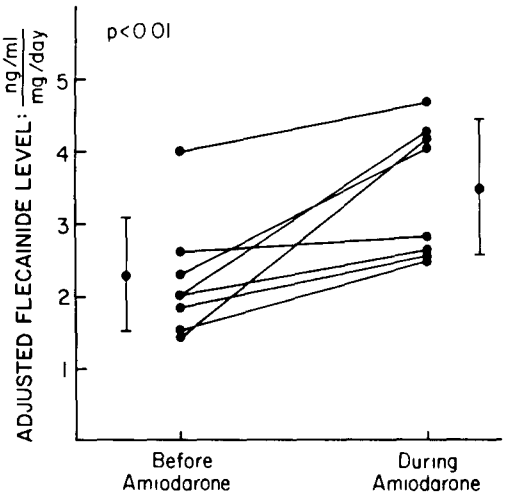


Figure 1. Dose-adjusted flecainide plasma levels measured before and during amiodarone therapy in eight patients.

levels were not systematically measured during this initial period of treatment. In one patient (Patient 8) flecainide was temporarily discontinued for 12 days while amiodarone treatment (600 mg/day) was begun, and then reintroduced in incremental doses.

Data analysis. Because flecainide doses were usually reduced at the time of amiodarone initiation, a direct comparison between flecainide plasma levels and dose ranges before and during amiodarone treatment was not made. Instead, all values of flecainide plasma levels were adjusted for the highest steady state daily dose of flecainide given before and during amiodarone therapy. Steady state was considered reached when the patient had received a regular dose of flecainide for at least 4 days (2). The dose-adjusted measurement was expressed as flecainide plasma level (ng/ml) per daily flecainide dose (mg). All flecainide level determinations were performed by either a gas-liquid chromatographic method (4) (Riker Laboratories Inc.) or a high performance liquid chromatographic method (5) (Roche Biomedical Laboratories, Inc.). All blood specimens were drawn immediately before drug administration. Most patients had conditions that remained stable throughout the study and required concomitant therapy with other medications. This was not controlled for in our study. However, no other drug was added to the patients' regimen at the time amiodarone therapy was begun. The dose-adjusted plasma flecainide levels recorded in each patient were compared before and during amiodarone therapy using the paired Student's *t* test. All results are reported as mean value ± SD.

Results

Plasma flecainide levels during amiodarone therapy. After the initiation of amiodarone treatment there was a rise in the mean dose-adjusted flecainide plasma level from 2.3 ± 0.8 before amiodarone to 3.4 ± 0.9 (ng/ml)/(mg/day) during amiodarone treatment ($p < 0.01$). This rise occurred in each patient (Fig. 1). The percent increase in dose-adjusted plasma flecainide levels measured during combination therapy ranged from 4 to 191% (mean = 60 ± 58, $p < 0.03$).

The daily doses of flecainide associated with steady state trough plasma flecainide levels before and during amiodarone treatment are recorded for each patient in Table 1. The average daily flecainide dose, when it was used as a single agent, was 325 ± 103 mg, as opposed to 225 ± 113 mg when it was used in combination with amiodarone ($p < 0.03$). These doses of flecainide produced average plasma levels of 690 ± 173 and 695 ± 220 ng/ml before and during amiodarone treatment, respectively ($p = 0.96$).

Time course of amiodarone-flecainide interaction. Sufficient data were not available in each patient to define an accurate time course of the drug interaction, particularly

Table 1. Daily Doses of Flecainide Associated With Steady State Trough Plasma Flecainide Levels Before and During Amiodarone Treatment

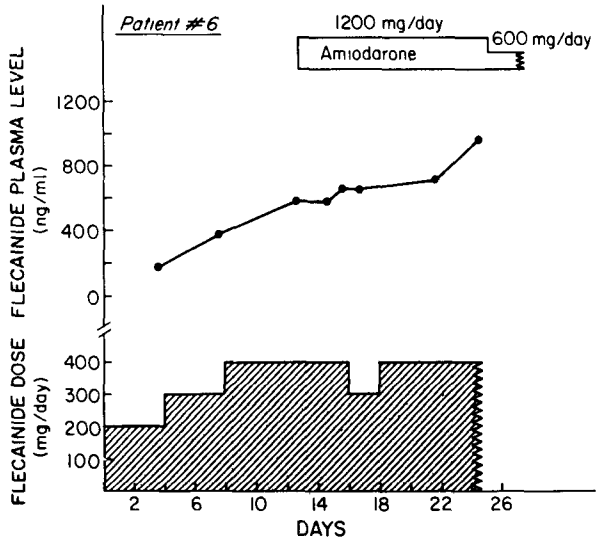
	Before Amiodarone			During Amiodarone			
Case	Flecainide Plasma Level (ng/ml)	Flecainide Dose (mg/day)	Number of Days on Dose	Flecainide Plasma Level (ng/ml)	Flecainide Dose (mg/day)	Number of Days on Dose	Number of Days on Amiodarone
1	790	300	4	550	200	10	14
2	920	500	4	505	200	114	124
3	790	200	4	462	100	4	19
4	696	300	4	597	150	21	32
5	498	200	4	835	200	4	83
6	590	400	5	970	400	6	12
7	418	300	4	610	150	65	72
8	816	400	150	1034	400	60	51
Mean ± SD	690 ± 173	325 ± 103		695 ± 220	225 ± 113		
			$p < 0.03$				

because the daily dose of flecainide was usually reduced at the time of initiation of amiodarone treatment to avoid potentially serious adverse side effects. In Patients 6 and 7, however, enough information was collected to give an estimate of this time course (Fig. 2 and 3). These data suggest that the interaction begins early after the onset of amiodarone treatment, and may take 2 weeks or more to fully manifest itself. Additional studies will be necessary to define this time course more accurately.

Discussion

Amiodarone-flecainide interaction and flecainide pharmacokinetics. Combining antiarrhythmic agents is a common medical practice, the value of which is supported more by theoretical considerations and pragmatic observations than by systematic trials. Amiodarone is frequently combined with other antiarrhythmic agents and is known to raise plasma levels of many drugs (3). Thus, the finding of an interaction between amiodarone and flecainide was no surprise, and because of the high likelihood of toxic complications we chose, in most patients, to reduce the dose of flecainide when amiodarone treatment was begun to avoid these complications. In multiple oral dosage studies of 16 subjects using the superposition method (2), calculated steady state plasma levels of flecainide, based on its known pharmacokinetics, were generally in agreement with the levels actually measured. Thus, the plasma pharmacokinetics of flecainide were found to be independent of dose or plasma concentration, and to be nearly linear with multiple oral dosage regimens. This allowed us to quantify, at least approximately, the interactive process in each patient by correcting the steady state plasma levels for the daily drug requirements before and during amiodarone treatment. Whether the pharmacokinetics of flecainide remain linear in the presence of amiodarone still needs to be studied.

Figure 2. Patient 6. Rise in flecainide plasma level after initiation of amiodarone therapy.



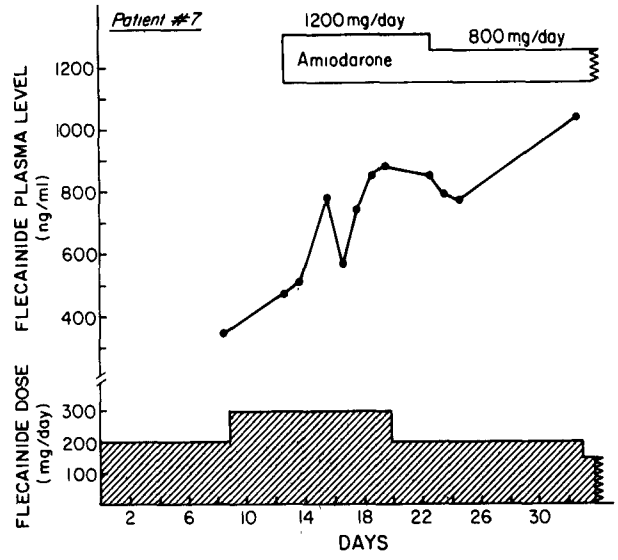


Figure 3. Patient 7. Rise in flecainide plasma level after initiation of amiodarone therapy.

Adjustment of flecainide dosage during combined therapy. The potential for serious adverse effects of this drug interaction was discussed by Fontaine et al. (6) and Leclercq and Coumel (7). These authors, who have treated many patients with the two drugs combined, suspected an interaction when they noted an increased incidence of cardiac decompensation, proarrhythmic complications and elevation of pacing threshold, adverse effects usually attributed to flecainide. Their observations led them to systematically reduce the dose of flecainide by half the usual amounts when combined with amiodarone, although no measurements of plasma levels were obtained to confirm their clinical impression. Our data suggest that reducing the daily dose of flecainide by one-third during combined treatment allows the maintenance of plasma levels in the range of those obtained with full doses of monotherapy. However, in view of the wide range of individual variations noted among our patients, it is imperative to measure serial plasma flecainide levels during the initial period of combined therapy to avoid toxic complications or, conversely, underdosing.

Possible mechanisms of amiodarone-flecainide interaction. The mechanism by which amiodarone elevates flecainide plasma levels has not been elucidated by this study. Before embarking on complicated systematic pharmacokinetic studies in a group of patients whose hospitalization was already lengthy and tedious, we felt an obligation to confirm the existence of an interaction. More than one mechanism of interaction may be operative; some possibilities include a decreased rate of enzymatic biotransformation from

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altered hepatic function, a decrease in renal elimination, a change in drug distribution, competitive protein binding and an increase in enteric absorption. The last two mechanisms seem unlikely, because flecainide is only approximately 40% protein bound and because its enteric absorption is nearly complete (2).

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